Rejection Under 35 U.S.C. § 101

Claims 23-29 are rejected by the Examiner under 35 U.S.C. § 101 for not being supported by either a specific and substantial asserted utility or a well established utility. Applicants respectfully request reconsideration and withdrawal of the rejection.

Instant Invention

The present invention is drawn to a method of identifying one or more compounds that modulate the function of C-RET receptor protein kinase. Alterations in the normal function of receptor protein tyrosine kinases (RTPKs) such as C-RET can result in an abnormal condition in an organism. Therefore, a goal of the instant invention is to determine receptor protein tyrosine kinase function in cells or tissues in order to gain control of the function of the RPTK.

The Examiner asserts that there is not a "well established utility" for the claimed invention. A "well established utility" is defined by the Examiner as a utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one of skill in the art. The Examiner indicates that the Specification discloses that C-RET is an "orphan receptor" and that C-RET is called an orphan receptor because no ligand has been identified which directly activates it. The Examiner asserts that the term "orphan receptor" refers to an RPTK without a known function. Therefore, the Examiner concludes that there is not a "well established utility" for the claimed invention.

Applicant asserts that there is a well established utility for the claimed invention. As noted below, the Specification sets forth utilities for the claimed invention, nevertheless,

Applicant also provides the following evidence of a well established utility. Applicant notes that a ligand (Glial Cell Line Derived Neurotrophic factor – GDNF) has been identified which directly activates C-RET. Additionally, it has been established that the biological pathway governing C-RET is involved in neuronal survival. On page 27, lines 3-6 of the instant Specification, for example, it states that C-RET is implicated in development and survival of enteric, sympathetic and sensory neurons upon stimulation by the ligand GDNF. Additionally, attached herewith are exemplary references illustrating that GDNF is a ligand for C-RET and the involvement of C-RET in neuronal cell survival. The references are Trupp, et al., *Nature*, 381(6585):785-789, 1996, Treanor, et al. *Nature*, 382(6586):80-83, 1996 and Jing, et al. *Cell*, 85(7):1113-24, 1996, Exhibits 1, 2 and 3, respectively.

On page 785, right column, lines 8-11 of Trupp et al., it states "Here we show that GDNF binds to, and induces tyrosine phosphorylation of, the product of the C-RET proto-oncogene, an orphan receptor tyrosine kinase..." On page 80, left column, lines 9-12 of Treanor et al., it states "We further demonstrate that GDNF promotes the formation of a physical complex between GDNFR-α and the orphan tyrosine kinase receptor RET, thereby inducing its tyrosine phosphorylation." Additionally, on page 1113, right column, lines 23-27 of Jing et al. it states "In this paper, we report the isolation of a novel cDNA clone for a high affinity GDNF receptor and the elucidation of its role in mediating the GDNF-induced autophosphorylation and activation of the RET receptor PTK."

Therefore, since GDNF is known to promote the survival and phenotype of central dopaminergic, noradrenergic and motor neurons, as well as various subpopulations of peripheral sensory and sympathetic neurons (see page 785, right column, lines 1-5 of Trupp et al.) and since Trupp et al., Treanor et al. and Jing et al. show that GDNF is a ligand for

C-RET, a well established utility for the instant invention is mediation of GDNF's effects on dopaminergic, noradrenergic and motor neurons (see page 785, right column, lines 17-19 of Trupp et al.). Moreover, the specification states that compounds that activate C-RET are useful for treatment of neurodegenerative disorders, such as Alzheimer's. See page 27. It is noted that the Specification also states that since over expression of ret is implicated in cancers, such as cancer of the thyroid, compounds that inhibit C-RET function are possible anti-cancer agents. See page 27.

The Examiner further indicates that the utilities asserted by the Applicant are not specific or substantial. A "specific utility" is defined by the Examiner as a utility that is specific to the subject matter claimed. A "substantial utility" is defined by the Examiner to be a utility that defines a "real world" use. The Examiner indicates that utilities that require or constitute carrying out further research to identify or reasonably confirm a real world use are not substantial utilities. The Examiner asserts that since neither the Specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the claimed C-RET, further experimentation is necessary to attribute a utility to C-RET.

Applicant asserts that the utilities of the instant invention are specific. On page 4, lines 4-6 of the instant specification it states "Because RPTKs control a variety of cellular functions, any alteration in the normal function of an RPTK can result in an abnormal condition in an organism." On page 4, lines 16-19 of the instant specification it states "Because alterations in the function of one RPTK can lead to a diseased state in an organism, determining the function of individual receptors is important for designing compounds that will prevent or treat these diseases." Additionally, in the examples on

pages 42-46 of the instant specification, cell survival is studied in connection to activation of C-RET. As discussed above, GDNF is known to promote the survival of neurons and GDNF is shown to be a ligand for C-RET. Therefore, one specific utility of the claimed invention is to control the survival of neurons with a compound that modulates C-RET function. One class of diseases that can be treated is neurodegenerative diseases such as Parkinson's disease. See, for example, page 27 of the instant specification. In addition, page 789, left column, lines of Trupp et al., states "New approaches for the treatment of [Parkinson's disease] and other neurodegenerative diseases may be developed by targeting Ret or the signaling pathway that is initiated when this receptor is activated."

Furthermore, Applicant asserts that the utilities of the instant invention are substantial. As discussed above, GDNF is a ligand that is known to interact with C-RET to induce tyrosine phosphorylation. Trupp et al. identifies one real world use for identifying such ligands, which is the treatment of Parkinson's disease and other neurodegenerative diseases. Treatment of these diseases also is discussed in the Specification. Therefore, no further research is necessary to identify a real world utility for the instant invention.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 23-29 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. As discussed in detail above, Trupp et

al., Treanor et al. and Jing et al. illustrate that GDNF is a ligand that interacts with C-RET to promote tyrosine phosphorylation. A real world use for identifying such ligands is the treatment of neurodegenerative diseases such as Parkinson's disease. See the Specification at page 27. Therefore, since the claimed invention is supported by both a specific and substantial asserted utility as well as a well established utility, one of skill in the art would know how to use the claimed invention.

CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the Examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If the Examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.